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INVITED COMMENTARY

Male Contraception

Better provision and marshalling of data needed to provide evidence of immunocontraception

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In the manuscript 'The preparation and application of N-Terminal 57 amino acid protein of the follicle-stimulating hormone receptor as a candidate male contraceptive vaccine' published in *Asian Journal of Andrology*, Xu *et al*.[1] concluded that a preparation of the human follicle-stimulating hormone receptor protein had potential to become an antigen for a human contraceptive that lacked hormonal side effects.

The rationale was that by choosing a 57 amino-acid sequence of the follicle-stimulating hormone receptor with low homology to the luteinizing hormone receptor as immunogen, endocrine changes would be minimized by the lack of antibody cross reaction to luteinizing hormone. Details of the construction, expression and production of the recombinant plasmid and antigen comprise a large part of the paper. The peptide was immunogenic and serum (but not seminal plasma) titres rose by 8 weeks after immunization, reached a maximum at 12 weeks and remained elevated to 16 weeks.

Although blood was sampled every 5 weeks from immunization, only hormonal data from weeks 0 to 8 (in the figure) or 12 (in the legend) were presented, although antibody titres had only risen above control values by week 8. The results revealed no alteration in luteinizing hormone, testosterone or estradiol levels in serum, consistent with their hypothesis. However, changes may well have occurred later when antibody titres had been elevated for longer, and should have been reported at the time of the fertility tests.

Semen was collected at the time of the last five blood collections, but, again, only one of the results was presented: the 16 week collection, when antibodies had been raised for 6 weeks. Although analyzed by World Health Organization methods, the World Health Organization preference for total ejaculated sperm numbers to reflect fertility was ignored. A 28% decrease in seminal sperm concentration in the immunized males was shown, but semen volumes were not given: had semen volume in these males been increased 1.4-fold, the total sperm count would have been the same as in the controls, and thus unable to reduce fertility. No significant changes in sperm motility or linearity of motion were detected at this time. Data from later times, particularly around the time of the mating tests, should have been included.

Histological studies of the testis, and statements on the blood-testis barrier, at the end of the study were uninformative, as no specific tests on the intactness of the blood-testis barrier (heavy metal exclusion or hyperosmotic spermatogonial shrinkage) were made. Despite being statistically significant, the difference in seminiferous tubule diameter of the immunized and control groups was small (4% larger in the former) and thereby of questionable biological significance.

The most relevant results for a contraceptive vaccine are those for fertility, and these were conducted at 24 weeks (when antibodies had been raised for 16 weeks). They revealed a 33% lower pregnancy rate in the females mated to the immunized males than in those mated to sham-immunized controls. As the authors state, these antifertility effects need to be improved, but just how this is to be achieved was not stated.

It would be comforting to know that the fertility decline was indeed due to the effect of the raised serum antibodies against the follicle-stimulating hormone receptor on sperm numbers; unfortunately, the separation in time of the analyses of hormones, semen and fertility cloud the overall picture. Was the antibody titre higher in the less fertile males? Was there a relationship between pregnancy rate and antibody titre? In time-course studies, what is happening can be clarified by analyzing all samples collected (why collect samples and not analyze them? or why analyze them and not present the results?), and presenting all results in parallel. Such a presentation would make it clear if the changes in antibody titre could have driven subsequent changes in hormones, semen quality and fertility. More comprehensive data collection and a more thorough and integrated analysis and presentation of the results could provide more convincing evidence that some extent of immune infertility had been achieved in this study.

Although the authors quote verbatim from Nieschlag and Henke (2005)[2] on the nature of the road to male contraception, they ignore the red flags raised in that article about the problems of immune responses in humans (such as local site reactions and irreversibility) that made the World Health Organization Taskforce on Male Fertility Regulation reject the immune approach,[3] and which also raise questions on the acceptability and effectiveness of immunocontraception.

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